REMARKS

I. Status of the Claims

With entry of this amendment, Claims 1-8, 10-18, 20, 21, 23-27, 29, 30, 32-40, 42-44, and 46-54 are pending. Claims 9, 19, 22, 31 and 45 have been canceled, without prejudice by the instant amendment. Claims 1-8, 10-18, 20, 21, 23-27, 29, 30, 32-40, 42-44, and 46-50 have been amended to correct technical and grammatical informalities and to more particularly point out the subject matter that applicants regard as the invention. New claims 51-54 are directed to a composition used in accordance with the method of claim 1. Full §112 support for these amendments can be found in the specification at page 3, line 28-30, page 4 line 1, page 9, lines 12-26, page 10, lines 1-18, and page 34, lines 14-30. No new matter has been added by the amendments. The amendments do not raise any new issues and thus, do not necessitate any additional search of the art by the Examiner.

II. Compliance with Sequence Listing Rules

The Examiner has objected to the specification for sequence listing informalities. On October 5, 2000, applicants submitted a Sequence Listing in compliance with 37 C.F.R. § § 1.821 *et seq*. With this amendment, applicants have revised the specification at page 31 to include sequence identifiers and to recite the sequences in the format required by the rules. Accordingly, the objection to the specification should be withdrawn.

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III. Claim Objections

Claim 17 has been amended to correct the clerical error previously contained in this claim. Claim 31 has been canceled. Accordingly the Examiner's objections to the claims have been overcome.

IV. Written Description Rejection under 35 U.S.C. § 112 First Paragraph

Claims 1-16 and 29-40, and 42-50 stand rejected under 35 U.S.C. § 112 first paragraph, for allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors had possession of the claimed invention at the time the application was filed. It is alleged that ES or EC, derived from species other than mice, are not disclosed in the specification and were not known in the art at the time the application was filed. Applicants respectfully traverse this rejection.

The amended claims recite embryonic stem cells (ES), embryonic carcinoma cells (EC), or embryonic gonadal cells (EG). Applicants direct the Examiner's attention to articles authored by Saito *et al.*,* Doetschman *et al.*,* Notaranni *et al.*,* and Sukoyan *et al.** which establish that embryonic stem cells from a variety of species including cow, hamster, pig, sheep and American mink were known in the art at the time the instant application was filed. Applicants direct the Examiner to an article authored by Pera *et al.** which demonstrates that human EC were also known in the art at the time the instant application was filed. Applicants clearly described the use of ES, EC or embryonic gonad (EG) cells (see *e.g.* page 3, line 28- page 4, line 1 of the specification)

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in the claimed methods and compositions. Based upon the state of the art at the time the application was filed, and the clear statements made in the specification, the skilled artisan would understand that the applicants were in possession of the claimed invention. Thus, the applicants have indeed satisfied the written description requirement of 35 U.S.C. § 112.

V. Enablement Rejection under 35 U.S.C. § 112 First Paragraph

Claims 1-27 and 29-40 and 42-50 stand rejected under 35 U.S.C. § 112 first paragraph as allegedly not enabled by the specification. The Examiner contends that the specification is not enabling for the use of "any and all pluripotent cells" derived from "any and all species." Applicants disagree. Without conceding to this basis of rejection, applicants have amended the pending claims to recite ES, EC or EG cells, thus obviating the rejection. Furthermore, applicants have submitted concurrently with this response, articles that demonstrate that ES, EC or EG cells from species other than mice were known in the art at the time of the instant invention. The specification clearly teaches the use of ES, EC, or EG cells (see e.g., page 3, line 28- page 4, line 1 of the specification).

The Examiner has cited to three documents (Moreadith *et al.* 1997, *J. Mol. Med.* 75:208; Seamark *et al.* 1994, *Reproduction, Fertility and Development* 6:653; and Mullins *et al.* 1996, *J. Clin. Invest.* 98 S37) which allegedly demonstrate that ES cells were known only in mice at the time this application was filed. This interpretation of the cited articles, however, is incorrect. The cited documents acknowledge the existence of ES cells in various species, (see Seamark p.654 column 2; Mullins p 38 column 1) but merely remark that the successful application of ES cells in the creation of transgenic

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animals had not been achieved. The references cited by the Examiner address a problem associated with an *in vivo* application of ES cells, **not** an ***in vitro*** application of ES, EC or EG cells as presently claimed. Thus, the Examiner's concern regarding enablement of the invention based upon the cell lines recited in the claims is without cause.

The Examiner has objected to the breadth of the method claims and alleges that the method claims are not enabled as a result of the claim breadth. The Examiner alleges that the second vector recited in the method claims must be able to be replicated extrachromasomally by any and all replication factors. This allegation has no merit. Paragraph (iii) of claims 1, 33 and 47 (and paragraph (ii) of claim 51) specifies that "extrachromasomal replication of the second vector is dependent upon presence within the cell of the replication factor." All of the other method claims depend from these claims. Thus, the method claims do not encompass any and all replication factors, but rather clearly indicate that the replication of the second vector is dependent upon the replication factor expressed by the first vector. The skilled artisan would understand that the replication factor encoded by the first vector must be specific for the replication of the second vector. The skilled artisan, therefore, would not have to engage in undue experimentation to practice the invention as claimed and therefore it is fully enabled.

The Examiner has objected to the breadth of the claims encompassing any and all functional variants, analogues and derivatives of the viral replication factor selected from polyoma large T antigen, EBNA-1 antigen, papilloma virus replication factors and SV40 large T antigen. Without conceding the correctness of the Examiner's rejection

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and for the sole purpose of expediting prosecution the applicants have amended the claims so that they no longer refer to functional variants, analogues and derivatives of the viral replication factor selected from polyoma large T antigen, EBNA-1 antigen, papilloma virus replication factors and SV40 large T antigen. This amendment obviates the rejection.

The Examiner alleges that claims which do not recite the limitation *in vitro* are not enabled by the instant specification and are overbroad and read on the unpredictable art of gene therapy. Without conceding the correctness of the Examiner's rejection and for the sole purpose of expediting prosecution the applicants have amended claim 33 to recite "*in vitro*". All claims now recite *in vitro* or depend upon claims which recite *in vitro* thus, obviating the Examiner's rejection.

VI. Rejection Under 35 U.S.C. § 112 Second Paragraph

Claims 3, 5, 6, 12-16, 24-27, 35, 37-40, and 42-50 stand rejected under 35 U.S.C. § 112 second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim that which the applicants regard as the invention.

Claims 2-16, 18-27, 30-32, 34-35, 38-40, and 42 -50 have been amended herein to recite "the" instead of "a" thus obviating the Examiner's rejection.

Claim 3 has been amended to delete reference to "functional variants, analogues and derivatives," thus obviating the rejection.

The Examiner contends that the phrase "the selectable marker is an antibiotic resistance gene" is unclear in Claims 5 and 27. These claims have been amended to recite "a gene product conferring antibiotic resistance," thus obviating the rejection.

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Claim 6 has been amended to delete the phrase "is adapted to receive a DNA," thus obviating the Examiner's rejection.

The Examiner contends that the phrase "the DNA codes for a polypeptide or protein" renders Claims 12, 13, 15, 24 and 25 indefinite. These claims have been amended to recite "second DNA," thus obviating the rejection.

Claims 14 and 26 are rejected because the phrase "the promoter is inducible" allegedly renders the claim indefinite. The Examiner contends that it is unclear to which promoter the phrase refers. Claims 14 and 26 have been amended to recite "the promoter of the second DNA," thus obviating the rejection.

Claim 16 is rejected because the phrase "replication of the second vector can be prevented by a site specific recombinase" is allegedly unclear. The Examiner contends that claim 16 fails to limit "expression of a DNA" recited in the preamble of claim 1. Applicants respectfully submit that this rejection is made in error and request that it be withdrawn. Claim 16 limits expression of DNA by limiting replication of the second vector. If the second vector does not replicate it will be lost in progeny cells and thus, not expressed. Therefore the claim does limit the expression of DNA as recited in the preamble to claim 1.

Claim 35 is rejected because the limitation "two factors" lacks antecedent basis. Claim 35 depends on claim 33 which recites only "replication factor". Claim 35 has been amended to recite "presence in the cell of a first test factor and a second test factor" thus, obviating the rejection. As suggested by the Examiner, Claim 35 has also been amended to substitute "or" for "and" in the description of the Markush group.

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Claims 37 and the respective dependent claims 39-50 are rejected because the phrase "investigating the properties of a DNA sequence " is allegedly unclear. Claim 37 has been amended to recite "an *in vitro* method of assaying whether a DNA under investigation codes for a polypeptide that directs transport of a cell active protein to a cell surface." The specific property of the DNA sequence to be investigated is now recited and the claim is no longer unclear, thus obviating the rejection.

Claim 39 is rejected because it is alleged that the term "disabling" is indefinite. The Examiner contends that the metes and bounds of the claim can not be exactly determined because the claim does not recite how the DNA is disabled. Applicants traverse. The term "disabling" is specifically defined in the specification on page 10, lines 7-17 as an alteration to a DNA sequence that is responsible for transportation of a protein to the cell surface. However, to expedite prosecution, Claim 39 has been amended to recite "such that the protein is not transported to the cell surface."

Claim 48 is rejected because step (a) allegedly lacks antecedent basis. Claim 48 depends on claim 37. Claim 37 does not recite a step (a). The dependency of claim 48 has been corrected by this amendment to recite claim 47. The amendment merely corrects a typographical error and thus obviates the rejection.

Claims 49 and 50 are rejected because there is no linking step between claims 49 and 50 and the independent claim 37 from which both claims 49 and 50 depend. Claim 49 is amended to specify that the DNA coding for a cell surface or secreted protein is identified by isolating the DNA under investigation. Claim 50 is amended to specify that the cell surface or secreted protein is identified by isolating the protein or

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polypeptide encoded by the DNA under investigation. The amendments obviate the rejection to claims 49 and 50.

VII. Rejections Under 35 U.S.C. § 102

Gassmann

Claims 1-5, 8-12, 17-23, 27 and 29-32 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Gassmann *et al.* 1995, *Proceedings of the National Academy of Science USA 92:1292*. This rejection is in error and the applicants respectfully request that it be withdrawn. Gassman does not teach all of the elements recited in claims 17-23, 27 and 29-32. Gassman does not teach a vector that contains a second DNA with a promoter for expression of the second DNA wherein the second DNA does not code for a selectable marker as required by claims 17-23, 27 and 29-32. The Examiner is respectfully reminded that to anticipate a claim a single source must teach all of the elements of a claim. M.P.EP. §§ 706.02, 2131; *Hybritec Inc. v. Monoclonal Antibodies Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Gassman does not teach every element of claims 17-23, 27 and 29-32 and thus, does not anticipate these claims.

Likewise, Gassmann does not teach all of the elements recited in claims 1-5 and claims 8-12. Gassman does not teach a second vector that contains a second DNA with a promoter for expression of the second DNA wherein the second DNA does not code for a selectable marker as required by claims 1-5, and 8-12 and therefore does not anticipate these claims. Furthermore, claim 1 is amended herein to recite "expressing the second DNA, thereby obtaining a gene product encoded by the second DNA". Claims 2-5 and 8-12 depend upon claim 1. Gassman does not teach expressing the

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second DNA, thereby obtaining a gene product encoded by the second DNA and therefore the rejection of claims 1-5 and 8-12 under 35 U.S.C. § 102(b) based upon Gassman is obviated by the instant amendment.

Carstens

Claims 17-22, 24-25 and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Carstens *et al.* 1995, *Gene* 164:195. Carstens teaches a vector containing an expression cassette driven by a CMV promoter enhancer and containing an EB*oriP* site. The replication factor, EBNA-1 protein, is supplied in *trans*. Claim 17 is amended herein to recite that the replication factor "is selected from the group consisting of polyoma large T antigen and papilloma virus replication factors". Claim 17 as amended is not anticipated by Carstens. Claims 18-22, 24-25 and 27 depend upon claim 17. Thus, the instant amendment obviates the rejection under 35 U.S.C. § 102(b) based upon Carstens.

Kobayashi

Claims 17-22, 25 and 27 stand rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Kobayashi *et al.* 1995, *Antisense Research and Development* 5:141. Kobayashi teaches an expression vector containing an expression cassette encoding anti-sense Rb-1 under the control of a CMV promoter and an SV40-*ori*. The SV40 large T antigen is supplied in *trans*. Claim 17 is amended herein to recite that the replication factor "is selected from the group consisting of polyoma large T antigen and papilloma virus replication factors". Claim 17 as amended is not anticipated by Kobayashi. Claims 18-22, 24-25 and 27 depend upon claim 17. Thus, the instant amendment obviates the rejection under 35 U.S.C. § 102(b) based upon Kobayashi.

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VIII. Rejections Under 35 U.S.C. § 103

Claims 1-12, 17-24, 27 and 29-35 stand rejected under 35 U.S.C. § 103 as being unpatentable over Gassmann *et al.* 1995, *Proceedings of the National Academy of Science USA 92:1292*. This rejection is in error and Applicants respectfully request that it be withdrawn. Gassmann does not establish a *prima facie* case of obviousness. A *prima facie* case of obviousness requires three elements. There must be some motivation either in the reference, or in the knowledge available to one of ordinary skill in the art, to modify the reference or to combine the teachings of several references. There must be a reasonable expectation of success in modifying the reference or combining the teachings of the references. Finally, the prior art reference (or references when combined) must teach or suggest all of the claim limitations. See M.P.E.P. § 2143.

Gassmann does not teach or suggest all of the claim limitations. Gassmann merely suggests the possibility that establishing plasmids as episomes in ES cells may find utility for a variety of studies of gene regulation. Gassmann does not teach or even suggest an *in vitro* method of obtaining a gene product by expressing a DNA in an ES, an EC or an EG cell. Thus, Gassmann does not make claim 1, or dependent claims 2-12 obvious. Gassmann does not teach a vector that does not express the replication factor or a fragment or a portion of the replication factor. Gassmann merely deleted 1249 bp of the large T gene coding sequence. A large portion of large T antigen remained in the Gassmann second vector (see figure 1b). Thus, Gassmann does not make claim 17, or dependent claims 18-24, 27 and 29-32 obvious.

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Gassman provides no reasonable expectation of success that the second vector taught by Gassmann could be used to express a second DNA. The second vector taught by Gassman, PGKhphΔLT20, is 6500 bp (see figure 1b). In order to express a protein using this vector an expression cassette would have to be inserted into the vector. This would, by necessity, result in a vector backbone of 9.5-10kb before any gene or DNA of interest is inserted, thus making the PGKhphΔLT20 vector taught by Gassmann unsuitable as an expression vector. It is well known in the art that an inverse correlation exists between vector size and expression efficiency. As proof of this principle applicants direct the Examiner's attention to an article by Kreiss *et al.* * The second vector of the instant invention, by contrast is 7687 bp including the heterologous sequence of interest (Figure 1). The size of the instant claimed vector is shown to be suitable for expression of a gene of interest. The same cannot be said for the second vector taught by Gassmann. There is nothing in Gassmann to suggest that the PGKhphΔLT20 vector could be used to episomally express a gene or DNA sequence of interest. Therefore, Gassmann does not provide any reasonable expectation of success in using the PGKhphΔLT20 vector to express a DNA molecule of interest. Because there is no reasonable expectation of success found in the prior art using the PGKhphΔLT20 vector, Gassmann does not make any of the claims of the instant invention obvious.

A skilled artisan would not be motivated to modify what Gassmann teaches, to attain the claimed invention. Gassmann should not be considered in a vacuum.

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Gassmann does not teach a second vector capable of expressing a foreign gene of DNA sequence of interest. Subsequent work by the same author teaches away from a two vector system for the expression of a heterologous gene or DNA sequence of interest. Applicants direct the Examiner's attention to an article authored by Camenisch *et al.*[*] that explicitly teaches a one vector episomal system to express a heterologous gene or DNA sequence of interest in ES cells.

Claims 1 and 14 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gassman *et al. supra*. in view of Cooper (U.S. Patent No. 5, 624,820). Applicants traverse.

Cooper merely teaches the use of an inducible promoter in an episomal plasmid expression system. Thus, Cooper does nothing to cure the deficiencies of Gassmann discussed above *(i.e.* the lack of reasonable expectation of success due to the size of the second vector in Gassmann, the failure of Gassmann to teach or suggest all of the elements of claim 1). The teachings of Cooper combined with Gassmann, therefore fail to establish a *prima facie* case of obviousness and the rejection should be withdrawn.

Claims 1 and 15 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gassman *et al. supra*. in view of Carstens *supra*. Applicants traverse.

While it is accurate to state that Carsten refers to the LoxP site in their episomal vector system, the Examiner is incorrect in asserting that this reference combined with Gassmann makes the invention of claims 1 and 15 obvious. Carsten conducted their experiments in the immortalized BB-5 cell line derived from human fibroblasts. There is

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no reasonable expectation of success that a site specific recombinase would work in the ES cell system. There is certainly nothing in either Carstens or Gassmann to suggest that using site specific recombinase would work in a stem cell. The Examiner is reminded that obvious to try is not the standard for analysis under 35 U.S.C. §103. *In re Geiger* 815 F.2d 686, 2 U.S.P.Q. 2d (BNA) 1276 (Fed. Cir. 1987). Furthermore, Carsten does nothing to cure the deficiencies of Gassmann discussed above *(i.e.* the lack of reasonable expectation of success due to the size of the second vector in Gassmann, the failure of Gassmann to teach or suggest all of the elements of claim 1). The teachings of Carstens combined with Gassmann, therefore fail to establish a *prima facie* case of obviousness and the rejection should be withdrawn.

Claims 17 and 26 stand rejected stand rejected under 35 U.S.C. 103(a) as being unpatentable over Carstens *supra*, or Kobayashi *supra*, in view of Cooper *supra*. Applicants traverse and respectfully request that the rejection be withdrawn. Claim 17 recites "a replication factor selected from the group consisting of polyoma large T antigen, and papilloma virus replication factor". Claim 26 depends upon claim 17. Carsten teaches a vector that contains an EB*oriP* and EBNA-1 is supplied in *trans* by the BB-5 cells. Kobayashi teaches a vector containing an SV40 *ori* and the SV40 large T antigen is supplied in *trans* by the Cos-7 cell line. Cooper teaches a single vector containing an inducible promoter, at least one papovavirus origin of replication and a DNA sequence encoding a mutant form of papovavirus large T antigen. A *prima facie* case of obviousness is not established by combining these three references. The three references combined do not teach or suggest all of elements of claims 17 and 26 and thus, do not make claims 17 and 26 obvious. None of the references cited by the

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Examiner teach a replication factor selected from the group consisting of polyoma large T antigen, and papilloma virus replication factor. Because the cited references do not establish a *prima facie* case of obviousness with regard to claims 27 and 26 the rejection should be withdrawn.

Claims 33 and 36 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Gassmann *supra* in view of Carstens *supra* or Cooper *supra*. Cooper refers to the use of a single expression vector containing an inducible promoter, at least one papovavirus origin of replication and a DNA sequence encoding a mutant form of papovavirus large T antigen and a DNA sequence of interest to screen for oncogenes or anti-oncogenes. Carstens refers to screening a cDNA library using a single vector that expresses a EB*ori*P in BB-5 cells that express EBNA-1. Neither Cooper or Carstens teach an *in vitro assay* performed in ES, EC or EG cells. Nor do Cooper or Carstens teach using a second vector to express a gene of interest. Gassmann does not teach an *in vitro* functional assay, but does teach a two vector system established in ES cells. The second vector taught by Gassmann is not capable of expressing a gene of interest because of its size. Cooper and Carstens teach that to successfully express a foreign gene or sequence of interest a cell line with a genomically integrated replication factor is necessary. Gassmann does nothing to contradict this. Therefore there would be no reasonable expectation of success in combining Gassmann with Carstens or Cooper because the second vector taught by Gassmann did not express a foreign protein in ES cells. At best, the combination of these documents make the claimed invention obvious to try. As noted above, this is not the appropriate standard under 35 U.S.C. § 103. *In*

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re Geiger supra. Thus, claims 33 and 36 are not obvious and the rejection should be withdrawn.

Claims 37-40 and 44-50 stand rejected 35 U.S.C. §103(a) as being unpatentable over Tashiro *et al.* 1993, *Science* 261: 600 in view of Carstens, *supra*, Gassmann *supra*, Williams *et al.* 1988, *Nature* 336:684 and Moreau *et al.* 1988, *Nature* 336:690. Applicants traverse.

The documents cited by the Examiner do not teach all of the limitations of the instant claimed invention. Tashiro refers to a method of screening libraries for signal sequences. The method relies on antibodies to Tac to detect proteins on the surface of Cos cells. Carsten suggests episomal expression of DNA overcomes problems associated with chromosomal integration. Gassman discusses episomal maintenance, but not gene expression, using a two vector system in ES cells. Williams notes that secreted LIF prevents differentiation of ES cells and Moreau identifies the complete sequence of LIF. LIF, however contains a signal sequence (see Moreau). Claim 37, as amended herein, requires that "the DNA of (b) does not code for a polypeptide that directs transportation of the cell active protein to the cell surface". Claims 38-40, and 44-50 depend upon claim 37. Thus, the references cited by the Examiner do not teach every element of the instant claimed invention. Therefore a *prima facie* case of obviousness has not been established and the rejection should be withdrawn.

It is well accepted law that a reasonable expectation of success in making the claimed combination must be found in the cited documents and not in the applicant's disclosure. *In re Vaeck* 947 F.2d 488, 20 U.S.P.Q.2d 1438(Fed. Cir. 1991). The documents cited by the Examiner do not provide a reasonable expectation of success in

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attaining the claimed invention. None of the documents cited demonstrate expression of a differentiation inhibitor in ES cells. In fact, none of the documents cited demonstrate an episomal expression of any protein in an ES cell. The vectors discussed in Gassmann were not suitable for expression of cloned genes. There is nothing in any of the documents cited by the Examiner that a protein of interest, especially one that inhibits differentiation, could be expressed in ES cells. The prior art does not provide a reasonable expectation of success in achieving the claimed composition and the rejection of claims 37-40 and 44-50 should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, applicants respectfully request the reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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Dated: March 18, 2002

By: E Stewart Mittler
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MARKED-UP VERSION OF AMENDED SPECIFICATION

3). To minimise potential steric interference by cloned proteins with IL6 binding and IL6R function, DNA encoding a synthetic flexible linker peptide was then added to the 5' end of the truncated IL6R. Two alternative linkers have been used: [gly gly gly gly ser gly gly gly gly ser] Gly Gly Gly Gly Ser Gly Gly Gly Gly Ser (aa 1-10 of SEQ ID NO. 4) and a linker containing FLAG epitope, [gly ser ASP TYR LYS ASP ASP ASP ASP LYS] Gly Ser Asp Tyr Lys Asp Asp Asp Asp Lys (SEQ ID NO. 2) (FLAG epitope [in upper case] is underlined). The sequence of these linkers is shown in Fig. 9. In each case, the linker sequence has been cloned in frame with IL6R and has two unique cloning sites (XhoI and NotI) at its 5' end, allowing the introduction of cDNA libraries, or specific cloned sequences, in a directional manner. The FLAG epitope is recognised by a commercially available monoclonal antibody (M2; available from IBI/Kodak) regardless of its position within a fusion protein, and will thus allow the expression levels of surface protein to be measured directly by immunocytochemistry.

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MARKED-UP VERSION OF AMENDED CLAIMS

1. (Twice Amended) An in vitro method of obtaining a gene product by expressing a DNA in a [pluripotent] cell selected from the group consisting of an ES cell, an EC cell, and an EG cell, comprising:

(a) (i) transfecting the cell with a first vector that expresses a replication factor; or

(ii) otherwise obtaining a cell that expresses or will express the replication factor; [and]

(b) transfecting the cell with a second vector, wherein

(i) the second vector contains a DNA coding for a selectable marker in operative combination with a promoter for expression of the selectable marker;

(ii) the second vector additionally contains a second DNA in operative combination with a promoter for expression of the second DNA, and which second DNA does not code for a selectable marker; and

(iii) extrachromosomal replication of the second vector is dependent upon presence within the cell of the replication factor, and

(c) expressing the second DNA, thereby obtaining a gene product encoded by the second DNA.

2. (Amended) [A] The method according to Claim 1, wherein the replication factor is a viral replication factor.

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3. (Twice Amended) [A] The method according to Claim 2, wherein the viral replication factor is selected from polyoma large T antigen, EBNA-1 antigen, papilloma virus replication factors, SV40 large T antigen [and functional variants, analogues and derivatives thereof appropriate to the cell species].

4. (Twice Amended) [A] The method according to Claim 1, wherein the second vector does not express the replication factor.

5. (Twice Amended) [A] The method according to Claim 1, wherein the selectable marker is a gene product conferring antibiotic resistance. [an antibiotic resistance gene.]

6. (Twice Amended) [A] The method according to Claim 1, further comprising transfecting the cell with a third vector, wherein the third vector contains a DNA[,or is adapted to receive a DNA,] in operative combination with a promoter for expression of the DNA, and replication of the third vector is dependent upon presence within the cell of the replication factor.

7. (Amended) [A] The method according to Claim 6, wherein the third vector expresses a selectable marker, which selectable marker is different [to] from that expressed by the second vector.

8. (Twice Amended) [A] The method according to Claim 1, wherein the cell is selected from the group consisting of a mammalian cell and an avian cell.

[9. A method according to Claim 1, wherein the cell is an embryonic cell.]

10. (Amended) [A] The method according to Claim [9] 1, wherein the cell is an ES cell.

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11. (Twice Amended) [A] The method according to Claim 1, for transfection of an ES cell wherein the ES cell of step (a) expresses polyoma large T antigen and the second vector comprises a natural target for polyoma large T antigen.

12. (Twice Amended) [A] The method according to Claim 1, wherein the second DNA codes for a polypeptide or protein.

13. (Twice Amended) [A] The method according to Claim 1, wherein second the DNA codes for an antisense RNA.

14. (Twice Amended) [A] The method according to Claim 1, wherein the promoter of the second vector is inducible.

15. (Twice Amended) [A] The method according to Claim 1, wherein transcription of the second DNA can be activated by a site specific recombinase.

16. (Twice Amended) [A] The method according to Claim 1, wherein replication of the second vector can be prevented by a site specific recombinase.

17. (Twice Amended) A vector for transfection of a [pluripotent] cell selected from the group consisting of an ES cell, an EC cell and an EG cell in vitro, wherein:

(i) the vector contains a DNA coding for a selectable marker in operative combination with a promoter for expression of the selectable marker;

(ii) the vector contains a second DNA in operative combination with a promoter for expression of the DNA, and which second DNA does not code for a selectable marker;

(iii) extrachromosomal replication of the vector is dependent upon presence within the cell of a replication factor selected from the group consisting of polyoma large T antigen and papilloma virus replication factors; and

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(iv) the vector does not express the replication factor or a fragment or portion of the replication factor.

18. (Amended) [A] The vector according to Claim 17, wherein the vector is a viral replication factor.

[19. A vector according to Claim 18, wherein the viral replication factor is selected from the group consisting of polyoma large T antigen, EBNA-1 antigen, papilloma virus replication factors, SV40 large T antigen and functional variants, analogues and derivatives thereof.]

20. (Twice Amended) [A] The vector according to Claim 17, wherein the vector is free of DNA coding for the replication factor or any part thereof.

21. (Twice Amended) [A] The vector according to Claim 17, for transfection of mammalian or avian cells.

[22. A vector according to Claim 17, for transfection of ES cells.]

23. (Twice Amended) [A] The vector according to Claim [22] 17, comprising a natural target for polyoma large T antigen.

24. (Twice Amended) [A] The vector according to Claim 17, wherein the second DNA codes for a polypeptide or protein.

25. (Twice Amended) [A] The vector according to Claim 17, wherein the DNA second codes for an antisense DNA.

26. (Twice Amended) [A] The vector according to Claim 17, wherein the promoter of the second vector is inducible.

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27. (Twice Amended) [A] The vector according to [any] Claim 17, wherein the selectable marker is a gene product conferring antibiotic resistance [an antibiotic resistance gene.]

29. (Twice Amended) An ES, EC or EG cell transfected with a first vector that expresses a replication factor and with a second vector according to Claim 17 wherein the replication factor maintains the second vector extrachromasomally.

30. (Amended) [A] The [mammalian] cell according to Claim 29 wherein said cell is a mammalian cell.

[31. An embryonic cell according to Claim 29.]

32. (Twice Amended) [A] The cell selected from an ES, EC or EG cell according to Claim 29, and differentiated progeny thereof.

33. (Twice Amended) An in vitro assay for the effect of a presence in a [pluripotent] cell, selected from the group consisting of an ES cell, an EC cell and an EG cell, of a protein or polypeptide or other product of DNA expression, comprising the steps:

(a) (i) transfecting the cell with a first vector that expresses a replication factor; or

(ii) otherwise obtaining a cell that expresses or will express the replication factor;

(b) transfecting the cell with a second vector, wherein

(i) the second vector contains a DNA coding for the protein or polypeptide or other product of DNA expression in operative combination with a promoter for expression of the DNA;

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(ii) the second vector also contains a DNA coding for a selectable marker in operative combination with a promoter for expression of the selectable marker; and

(iii) extrachromosomal replication of the second vector is dependent upon presence within the cell of the replication factor;

(c) selecting for cells that have been transfected with the second vector; and

(d) maintaining the selected cells over a plurality of generations so as to assay the effect of expression of the protein or polypeptide or other product of DNA expression.

34. (Amended) [An] The assay according to Claim 33, wherein step (a) is carried out once and the cells obtained are divided and used for a plurality of separate assays in which steps (b)-(d) are carried out a plurality of times with second vectors containing different DNA sequences.

35. (Twice Amended) [An] The assay according to Claim 33, for assay of the effect of simultaneous presence in the cell of a first test factor and a second test factor, wherein said first and second test factors are independently selected from the group consisting of [presence in the cell of two factors, each factor being independently selected from] a protein, a polypeptide and another product of DNA expression.

37. (Twice Amended) [A] An in vitro method of assaying whether a DNA under investigation codes for a polypeptide that directs [transportation] transport of a

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cell active protein to a cell surface [investigating the properties of a DNA sequence] comprising expressing in a [pluripotent] cell selected from the group consisting of an ES cell, an EC cell and an EG cell a composite DNA including (a) [the] a DNA sequence under investigation, linked to (b) a DNA coding for [a] the cell active protein, wherein

(i) activity of the cell active protein is dependent upon transport of the cell active protein to the cell surface,

(ii) the DNA of (b) does not code for a polypeptide that directs [transportation] transport of the cell active protein to the cell surface, and

(iii) the cell active protein inhibits differentiation of the cell and in the absence of the cell active protein the cell will differentiate.

38. (Amended) [A] The method according to Claim 37, for screening a library of DNAs to identify DNA sequences coding for signal polypeptide sequences that transport proteins to the cell surface, and the method optionally comprises determining whether the cell active protein is transported to the cell surface and remains there or is secreted by the cell.

39. (Twice Amended) [A] The method according to Claim 37, wherein the DNA of (b) is obtained by deleting or disabling, from a DNA encoding a cell surface or secreted protein, that portion of the DNA that codes for the polypeptide sequence responsible for transportation of the protein to the cell surface such that the protein is not transported to the cell surface.

40. (Twice Amended) [A] The method according to Claim 37, wherein the cell active protein induces a morphological or proliferative change in the cell.

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41. [Cancelled]

42. (Twice Amended) [A] The method according to Claim 37, wherein the cell active protein is a cell surface receptor.

43. (Amended) [A] The method according to Claim 42, wherein the cell active protein is an IL-6 receptor and the DNA of (b) encodes a modified form of the receptor preprotein lacking a functional signal sequence.

44. (Twice Amended) [A] The method according to Claim 37, comprising investigating the properties of a DNA in mammalian or avian cells.

[45. A method according to Claim 37, comprising investigating the properties of a DNA in embryonic cells.]

46. (Amended) [A] The method according to Claim [45] 37, comprising investigating the properties of a DNA in ES, EC or EG cells or differentiated progeny of such cells.

47. (Twice Amended) [A] The method according to Claim 37, comprising expressing the composite DNA by :

(a) (i) transfecting the cell with a first vector that expresses a replication factor; or

(ii) otherwise obtaining a cell that expresses or will express the replication factor;

(b) transfecting the cell with a second vector, wherein

(i) the second vector contains the composite DNA in operative combination with a promoter for expression of the composite DNA;

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(ii) the second vector also contains a DNA coding for a selectable marker in operative combination with a promoter for expression of the selectable marker; and

(iii) extrachromosomal replication of the second vector is dependant upon presence within the cell of the replication factor;

(c) selecting for cells that have been transfected with the second vector; and

(d) maintaining the selected cells over a plurality of generations so as to assay the effect of expression of the composite DNA.

48. (Twice Amended) [A] The method according to Claim [37] 47, wherein step (a) is carried out once and the cells obtained are divided and used for a plurality of separate methods in which steps (b)-(d) are carried out a plurality of times with second vectors containing different DNA sequences.

49. (Twice Amended) [A] The method according to Claim 37, for identification of a DNA coding for a cell surface or secreted protein comprising isolating the DNA under investigation.

50. (Twice Amended) [A] The method according to Claim 37, for identification of a cell surface or secreted protein comprising isolating a protein or polypeptide encoded by the DNA under investigation.

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